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ABSTRACT

Concerned with clarifying some of the more complex issues in drug abuse, the National Clearinghouse for Drug Abuse Information has prepared this special report on narcotic antagonists, particularly nalorphine, naloxone, cyclazocine, levallorphan, and pentazocine. Background information is provided through a summary of their history, legal status, and the opinions of authorities in the field. Significant research on the subject is presented together with major findings on various aspects of the problem. The pharmacology, chemistry, clinical effects, treatment, and patterns of use of the drugs are dealt with. Bibliographic references are also listed. (BL)

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NATIONAL CLEARINGHOUSE FOR DRUG ABUSE INFORMATION

SERIES 26, NO. 1

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The National Clearinghouse for Drug Abuse Information recognizes the need for clarifying some of the more complex issues in drug abuse by gathering the significant research findings on each subject and developing fact sheets on the problem. These fact sheets, which are part of the Clearinghouse Report Series, present information about treatment modalities, the pharmacology and chemistry of the various drugs of abuse, and opinions and practices of recognized authorities in the field. This publication was researched and written by James R. Gamage and E. Lief Zerkin of the Student Association for the Study of Hallucinogens (STASH), Beloit, Wisconsin, under Contract No. HSM-42-72-231.

NARCOTIC ANTAGONISTS

Over the past decade a considerable amount of research energy has been focused on a class of compounds known as narcotic antagonists. These drugs, which often produce analgesia without some of the more undesirable actions of morphine, are showing promise in the management of heroin addiction.

History

The history of the narcotic (or opioid) antagonists dates back to 1915 when J. Pohl, a German, first demonstrated that N-allylnorcodeine effectively antagonized morphine-induced respiratory depression in rabbits and dogs. Although Pohl's discovery was potentially of great medical significance, it sparked no further research until 1941 when E. L. McCawley and his colleagues, hoping to discover a potent analgesic that would not cause respiratory depression, synthesized N-allyl-O-allylnormorphine.

One year later, J. Weijlard and A. E. Erickson (1942) achieved the synthesis of nalorphine and K. Unna (1943) outlined the drug's ability to reverse the respiratory and other pharmacological actions of morphine. In the early 1950's, further investigations showed that nalorphine was also capable of antagonizing the effects of other narcotics. Finally, in 1951, some 36 years after Pohl reported his unique discovery, an antagonist, nalorphine, was finally introduced into clinical medicine for the

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purpose of treating narcotic overdoses. In subsequent trials, nalorphine and other antagonists were usefully employed in the prevention of narcotic-induced respiratory depression of the mother and infant in obstetrics, for postoperative pain relief, for the diagnosis of narcotic addiction, and as aids in the management of post-withdrawal addicts.

It was Abram Wikler who, in 1965, first provided the rationale for the use of antagonists in the management of narcotic addiction. In an article entitled, "Conditioning Factors in Opiate Addiction and Relapse," Wikler attempted to account for the fact that detoxified addicts often report a craving for narcotics as soon as they return to their environment. These ex-addicts, despite the fact that they demonstrated no measurable "hunger" for, or dependence on narcotics in any clinical setting, usually felt their craving return once they returned to the "street."

When the addict becomes conscious of tensions or discomforts in his life situation, Wikler theorizes, he seeks and obtains relief from narcotics. The narcotics, because they afford him a pleasurable response, condition the addict to repeat drug-taking behavior, reinforcing his physical dependence. This dependence is further reinforced when the addict's failure to continue self-administration results in the anxiety and discomfort which accompany withdrawal. Once the addict enters a treatment program and undergoes withdrawal, he enters the phases of "physiological disequilibrium" and "conditioned abstinence." These states may persist well beyond the point at which his body has shed any physical need for narcotics. The addict, in a sense, remains highly conditioned to the environment in which he freely self-administered narcotics, even though he may no longer be physically conditioned to the drugs themselves. When he is returned to "the street scene," he then responds to the old stresses and tensions with the only behavior he knows will afford relief: using narcotics.

According to one prominent researcher in the field, Dr. F. F. Foldes (1964), "This view of the relapse of addicts led to the suggestion that drugs which block the relief afforded by narcotics during 'conditioned abstinence' may lead to the extinction of physical dependence and conditioned drug-seeking behavior." If a detoxified addict is returned to his old environment while undergoing treatment with a narcotic antagonist, he will receive no gratification from any use of heroin and will be more able to extinguish his old drug-seeking behavior pattern if he acquires new modes of functioning.

Chemistry

Although there are a large number of compounds that are more or less capable of antagonizing the depressant and other pharmacological effects of narcotics, further discussion will be restricted to five main representatives of this class of drugs: nalorphine, naloxone, cyclazocine, levallorphan, and pentazocine. Four of these antagonists are derivatives of narcotic analgesics: nalorphine is an N-allyl derivative

of morphine, naloxone is an hydroxylated N-allyl derivative of morphine, cyclazocine is a cyclopropylmethyl derivative, and pentazocine is a dimethylallyl derivative of phenazocine. The first two compounds are examples of the generalization that the substitution for the methyl (CH_3) group of the basic nitrogen of narcotic analgesics with an allyl (CH_2-CH=CH_2) group results in a compound having antagonistic actions.

Pharmacology

Morphine is the prototype agonist. All its actions, including analgesia, tranquilization, salivation, constipation, and other direct effects are called agonistic. When these effects are reversed by other drugs, this is an antagonistic type of action. The drugs nalorphine (Nalline), pentazocine (Talwin), cyclazocine, and others are called partial antagonists for two reasons: (1) When they are administered to an individual whose body does not contain an opiate, they have analgesic properties (and others) like morphine, which are their agonist properties; and, (2) When they are administered to persons who are dependent, tolerant or have opiates in their body, they reverse all of the effects of morphine-like compounds and can bring on all the signs of abstinence (withdrawal) within minutes. Naloxone, a pure antagonist, has little if any action on the normal individual at reasonable doses. When given in such doses to a person dependent on narcotics, however, abstinence signs appear at once.

Respiratory Effects

There is some evidence to suggest that the narcotic antagonists may have a greater affinity for the morphine receptors of the respiratory center than for "sensory" (i.e., analgesic) morphine receptors. Conversely, morphine and other narcotic analgesics seem to attach themselves more readily to sensory receptors. Consequently, moderate doses of narcotic analgesics will produce relief from pain without severe respiratory depression. However, when the dose of a narcotic is greatly increased, more respiratory receptor sites will be occupied and the increased analgesia will be accompanied by severe respiratory depression. In cases of narcotic overdosage, the administration of an antagonist which will displace morphine from respiratory receptor sites, can avert death from respiratory failure.

Partial Narcotic Antagonists Effects

When partial narcotic antagonists are administered alone, some of their pharmacological actions are similar to those of narcotics, while others are different. In the following discussion the pharmacological actions of nalorphine will be outlined as representative of the other drugs in this class.

Nalorphine displays only minimal analgesic action in most test animals, with the exception of the rat. In man, however, nalorphine is, milligram for milligram, as potent an analgesic as is morphine. Levallorphan in doses capable of reversing narcotic-induced respiratory depression, has only negligible analgesic activity.

Cyclazocine, in moderate doses (2 mg., parenterally) produces analgesia equivalent to that seen after 10 mg. of morphine. With respect to analgesia, then, naloxone and levallorphan act more like true antagonists, while nalorphine and cyclazocine (along with pentazocine) are partial agonists.

Nalorphine has agonist actions on the gastro-intestinal tract, the circulatory system and the spinal cord. Nalorphine, like morphine, is also capable of inducing marked respiratory depression in man--this is also true for cyclazocine and levallorphan. In terms of these criteria, naloxone is more of a pure antagonist because when given alone, it does not induce respiratory depression.

Nalorphine is absorbed more rapidly than is morphine after subcutaneous administration. The drug also penetrates into the brain three to four times more rapidly than does morphine. Most narcotic antagonists have been found to penetrate the placental barrier, but their effects on the human fetus have not been systematically investigated. Nalorphine and levallorphan are excreted rapidly, primarily in the urine. These two drugs, along with naloxone, have a much shorter duration of action than their parent compounds. Cyclazocine, like other drugs in the benzomorphan series, has a much longer duration of action--1 mg. of the drug given orally still has a small but demonstrable blocking effect on the actions of 25 mg. of subcutaneous heroin given 12 hours later.

Foldes and his colleagues (1964) contend that tolerance and physical dependence do not develop to the pharmacological effects of nalorphine. However, Isbell (1956) and Martin and Gorodetzky (1965) observed that the unpleasant subjective effects of nalorphine were dissipated following a slow elevation of the dosage of the drug over a period of time. The same authors also describe an abstinence syndrome which develops in subjects given nalorphine for 45 days. One day after abrupt withdrawal of the drug the following signs and symptoms were observed in most subjects: yawning, lacrimation, rhinorrhea, perspiration, gooseflesh, restlessness, diarrhea, sleepiness, poor appetite, twitching and myoclonic jerks, weakness, headache, nausea, chills, shocks, back pains, itching, dizziness and ringing in the ears. In terms of tolerance and physical dependence, then, nalorphine seems to share some of the agonist properties of morphine, although the overall intensity of nalorphine's effects in the realm have been described as mild.

Like nalorphine, cyclazocine also seems capable of enduring physical dependence. In one human study, the drug was given in doses ranging from 0.4 to 13.2 mg./ 70 kg. per day for 70 to 104 days. After this period of administration, the abrupt withdrawal of cyclazocine produced a definite abstinence syndrome which more closely resembled that observed after nalorphine than the syndrome seen in cases of morphine or heroin addiction.

Abrupt withdrawal after chronic administration of pentazocine (a weak narcotic antagonist) also produces a definite abstinence syndrome in man, characterized by perspiration, insomnia and increased pulse rate and bowel movements. According

to Fraser and Rosenberg (1964), however, the syndrome is only about one-third as severe as that following abrupt withdrawal of morphine.

In contrast, naloxone does not induce respiratory depression when given alone and its prolonged administration has not been observed to produce an abstinence syndrome upon abrupt withdrawal. Tolerance to the antagonistic properties of naloxone has not been observed after long-term administration.

Clinical Effects

By far the most important clinical effect of the antagonists is their ability to reverse the respiratory and other actions of narcotic analgesics. This reversing ability has been found to be clinically useful in the management of narcotic overdoses, the detection and diagnosis of illicit narcotic usage, and may show promise of developing into an effective modality for the management of post-withdrawal addicts.

Use in Narcotic Overdosage

One of the major side effects of an excessive dose of narcotics is the depression of the respiratory centers of the brain. The arresting of respiration can be fatal and is the most common cause of mortality among naive, and even some experienced heroin addicts. The variability of the dosages illegally purchased by the addict increases his possibilities of overdosing. While small doses of narcotics cause analgesia, euphoria and other sought-after effects by addicts without massive interference with respiration, large doses may cause the development of coma, occasional convulsions and death from respiratory depression.

The narcotic overdose syndrome is usually so serious that, by the time the patient is seen by the physician, immediate measures must be taken in order to avoid death. Ever since nalorphine was introduced into clinical medicine by Eckenhoff and his colleagues (1951), for the purpose of reversing respiratory depression in narcotic overdoses, the use of antagonists has been established as the treatment of choice. In typical cases, small amounts of nalorphine (3 to 5 mg.) or levallorphan are given intravenously over the course of 20 to 30 minutes. The response of the comatose addict is usually so predictable that, according to Jaffe (1965), if no dramatic improvement is seen after a total of 15 to 20 mg. of nalorphine has been administered, "one can reasonably question the accuracy of the diagnosis."

Two major precautions are in order with respect to the use of nalorphine or levallorphan in the reversal of narcotic overdoses. First, narcotic antagonists will not reduce, and may even exacerbate, respiratory depression induced by alcohol or barbiturates. If the presenting case is one of mixed overdose and the role of narcotics in inducing respiratory depression is unclear, the use of naloxone (which has just recently been licensed for clinical use by the FDA) may be indicated since this drug produces no respiratory depression itself. The second precaution concerns the ability of all antagonists to induce severe withdrawal syndromes when given to

confirmed addicts. Once induced by an antagonist, a withdrawal syndrome may be extremely difficult to reverse, and in some situations the withdrawal syndrome can be more life-threatening than the narcotic-induced respiratory depression itself. To avoid this eventuality, it is usually recommended that antagonists be administered in a series of small doses over a period of 15 to 30 minutes. Care must also be taken to observe the patient periodically after he has been revived by an antagonist, for the duration of action of the antagonist may be shorter than the duration of action of the narcotic which initially caused the respiratory depression. This is especially true in the case of methadone overdose, where respiratory depression may reappear after the effect of the antagonist wears off.

Use in Detection of Narcotic Drug Abuse

The ability of narcotic antagonists to precipitate abstinence syndromes in addicts has been used in civil commitment and many probation programs to detect surreptitious use of heroin or other narcotics by prisoners. The procedure, called the "Nalline Test" (after the trade name for nalorphine), involves the administration of a small amount (2 to 3 mg.) of nalorphine subcutaneously and the subsequent measurement of pupil size. If the subject has not self-administered any opiate recently (48 to 72 hours prior to the test), his pupils will constrict slightly. On the other hand, if he has engaged in opiate use, his pupils will dilate and he may even exhibit some signs of abstinence if his prior use has been regular. Although the Nalline Test has been routinely employed in the criminal justice system in this country, Grupp (1970) has suggested that its reliability as a tool for controlling and detecting relapse into narcotics use is too variable to make it an accurate test.

Use in Management of Post-Withdrawal Addicts

As was mentioned above, the rationale for the use of antagonists in the management of post-withdrawal addicts was originally supplied by Wikler's conditioning theory of narcotic addiction. Nalorphine was first suggested for clinical trials in the blockade of heroin effects in ex-addicts, but its short duration of action and its elicitation of unpleasant subjective effects made the drug's long-term employment unfeasible.

In 1966, Martin suggested the use of the longer-acting antagonist, cyclazocine, as a more viable alternative drug. Clinical trials by Jaffe and Brill (1966) disclosed that although disturbing side effects emerged with the effective daily dose ot 4 to 6 mg., these were diminished with the development of tolerance. It was established however, that tolerance did not readily develop to the narcotic antagonist properties of cyclazocine.

Over the course of the next several years, some 450 post-withdrawal narcotic addicts were treated with cyclazocine in different areas of the United States. Fink and his colleagues (1971) at the New York Medical College studied the effects of cyclazocine blockade on 74 detoxified addicts. Each of the addicts was detoxified

using rapidly decreasing amounts of methadone. After a drug-free period of 7 to 10 days, necesssary to permit laboratory tests, cyclazocine was begun at 0.2 mg. per day orally. The dosage was increased by 0.2 mg. each day for 10 days, and if the patient appeared able to tolerate it, the quantity of cyclazocine was elevated by .04 mg. per day for 5 more days. In 14 days, the maintenance dose of 4.0 mg. per day was usually achieved. After the patients had been stabilized on a dosage of 4.0 mg. per day for a period of one week, they were presented with a "challenge" dose of 15 mg. of intravenous heroin. The patients who received challenges less than 6 hours after their last dose of cyclazocine usually reported no recognizable euphoric effects from the heroin injection. Patients who received heroin challenges 24 hours after their last dose of cyclazocine, however, were more likely to report heroin-like euphoria (6 out of 18). In most cases it was found that cyclazocine in a dosage of 5 mg. per day was completely effective in blocking the subjective effects of heroin for up to 24 hours. Over a period of 5 months of cyclazocine treatment (4.0 mg. per day), no tolerance developed to the blocking action of the drug.

At one year follow-up, 15 of the 74 patients had continued in rehabilitation for periods ranging from 5 to 16 months, and all of the 15 were found to be in school or working. Of the remaining subjects, 11 had discontinued cyclazocine and had volunteered for methadone, and 48 had returned to heroin use. Fink and his colleagues concluded that the need for intensive after-care, re-education, and rehabilitation measures is enhanced by cyclazocine. The patients who remained on cyclazocine reported an increase in sexual activity, an increase in time spent going to parties, dances, and in dating, an increased amount of interaction with non-addicts, and a reduction in anxiety and drug-seeking behavior. It was noted, however, that while cyclazocine serves to inhibit interest in narcotics, it has little if any effect on the patient's desire to use marihuana, alcohol, barbiturates, amphetamines, and tranquilizers.

In another major study at the Illinois Drug Abuse Program in Chicago, Chappel, Jaffe and Senay (1971) gave cyclazocine to 33 narcotic addicts who were attempting to remain abstinent from the use of illicit drugs. In contrast to earlier studies, which had used only self-selected addict volunteers, the Chicago researchers compared their results with cyclazocine patients with the outcomes of addicts in a non-cyclazocine control group.

The subjects were initially withdrawn from narcotics over a period of 2 to 10 days using decreasing doses of methadone. After testing with nalorphine to insure the absence of any physical dependence on narcotics, the cyclazocine subjects were given increasingly larger doses until they reached daily levels of 4.0 to 6.0 mg. At the end of 14 months, 46 percent of the cyclazocine patients were still in after-care treatment, and at the end of 20 months, 38 percent were in abstinence treatment. In contrast, only 11.8 percent of the non-cyclazocine withdrawn patients were abstinent after 14 months, and only 8.5 percent were abstinent at 20 months.

The authors, Chappel et al., conclude that cyclazocine appears to be a useful adjunct in the treatment of addicts who voluntarily choose to be withdrawn from

narcotics and want help in their attempt to remain abstinent, or for whom methadone may be inappropriate. They stress, however, that their study was not properly controlled and that the observed higher level of abstinence on the part of the cyclazocine patients may have been due to individual patient motivation, extra attention from the staff, or the fact of receiving something "special" and "oral" every day. They further emphasize that cyclazocine is not a maintenance drug (only 1 of their patients took it for more than 6 months--primarily for the drug's antidepressant actions) and that its primary usefulness may be in reducing the extreme anxiety and depression which so often characterizes the first few post-withdrawal months.

From the results of the above two studies and those conducted by Martin and Gorodetzky (1967), Jaffe and Brill (1966), Petursson and Preble (1970), and Resnick and his colleagues (1970), it appears that cyclazocine holds promise as a therapeutic tool because of its moderately long duration of action (12-14 hours), because of its relative acceptance by the addict population, and because of its possible antidepressant actions. Cyclazocine, however, in a large segment of the addicts to which it is administered, does induce unpleasant side effects such as dizziness, headaches and LSD-like hallucinations (though these reactions usually, but not always, disappear when tolerance develops).

These problems concerning the pharmacological unacceptability of cyclazocine on the part of some addicts prompted Fink and his colleagues (1968) to investigate the feasibility of utilizing naloxone in antagonist therapy. As a relatively pure antagonist, naloxone produces none of the respiratory or other morphine-like effects of cyclazocine; neither does it elicit an abstinence syndrome following abrupt withdrawal. Unlike cyclazocine and nalorphine, naloxone elicits no specific changes in EEG recordings. The only side effect observed in a pilot study with dosages of naloxone as high as 200 mg. per day was slight depression, which was abated by reducing the dose.

Alongside these apparent advantages, however, there are some serious drawbacks. The duration of naloxone-induced narcotic blockade is only 4 to 6 hours with normal doses and up to 200 mg. per day is required to achieve antagonism of heroin for 24 hours. Naloxone is also very poorly absorbed by the oral route; while only 1 mg. of intravenous naloxone is required to effectively block the effects of 40 mg. of intravenous heroin, 100 mg. of the drug administered orally is required to achieve the same effect. A further disadvantage is that naloxone is a very costly compound to produce: it must be synthesized from thebaine, which is present in very small quantities in raw opium.

Following their acute trials with naloxone, the research group at the New York College of Medicine conducted long-term studies of the effects of the drug in nine male volunteers. In the later study, the researchers attempted to greatly increase the daily doses of naloxone given to the detoxified addicts from 200 mg. per day to 1,200 and 2,400 mg. per day. In two subjects who received 400 mg. per day, antagonism to 25 and 50 mg. of intravenous heroin was found to persist for 6 hours.

When the daily dose was elevated to 800 mg., no response to the heroin injections was observed for up to 18 hours. In an attempt to extend the duration of naloxone blockade to 24 hours, 1,500 mg. per day was administered to two subjects, both of whom reported no response to the heroin challenge at 24 hours. However, two subjects who received daily doses of 2,400 mg. of naloxone showed only partial blockade to 25 mg. of heroin after 24 hours. Only one subject (who received 1,500 mg. per day) reported any discomfort--he complained of psychic depression, apathy and decreased appetite. Reduction of the dosage to 1,200 mg. per day controlled these symptoms effectively.

In general, though, the above studies of large, single daily doses of orally administered naloxone demonstrate the drug's ability to antagonize opiate challenges for 24 hours without secondary effects. The necessity of employing such large doses, coupled with the prohibitive cost of naloxone, however, may severely limit the drug's future applicability to large-scale treatment programs.

Current Research

Current research in the field of narcotic antagonists is focusing on the development of compounds with longer durations of action than naloxone or cyclazocine. Recent interest has centered on cyclorphan and n-allyl opiate derivatives and, according to one source, a derivative of naloxone, N-cyclopropylmethylnoroxymorphone (naltroxone), with twice the duration of action of the parent compound, is already undergoing preliminary tests in humans at the Addiction Research Center in Lexington, Kentucky.

Other investigators are studying a new delivery system for currently available antagonists which would extend their durations of action over considerable periods. The system centers around a device called a silastic capsule (made from silicone and rubber), which, depending upon thickness, can release a sustained dose of a drug over a period of months or even years. A limited amount of research has already been carried out to demonstrate the feasibility of administering drugs by this method. In one case, investigators at the Rockefeller Foundation Population Council were able to implant silastic capsules containing the contraceptive steroid Norgesterol in 500 women. By varying the thickness of the capsule and the amount of material in it, total contraceptive action was effected in these women for up to 500 days.

A silastic capsule, filled with enough of a narcotic antagonist to ensure blocking action against heroin effects for a year could conceivably be implanted in detoxified addicts using a trocas (a tube which has the gage of a large hypodermic needle). The capsule may be implanted in almost any body area (arms, legs, etc.), it causes minimal tissue damage, and several capsules could be implanted to effect almost any desired duration of action. The only possible danger to the patient is that of the capsule rupturing which, if it occurred, would release a toxic dose of the antagonist into the body.

The rapid development of the therapeutic potentials of the antagonists is now receiving high priority from the White House Special Action Office for Drug Abuse Prevention. According to a lead article in Science, $524,000 was invested in antagonists in fiscal 1971 and this amount appears likely to be increased in the near future. Critics of antagonist therapy have charged that the present infatuation with attempting to treat drug addiction medicinally, rather than by education preventive measures, shows "more concern for the welfare of society than for the welfare of the patient." Advocates of the antagonists contend, on the other hand, that these drugs can play an important role in helping addicts resist the "impulse fix" once they are returned drug-free to their natural environment.

Legal Aspects

Of the antagonists discussed above, nalorphine, naloxone and levallorphan are regulated by Federal law through their inclusion in schedules of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (Public Law 91-513). The antagonists, cyclazocine and pentazocine are not covered by this law, although cyclazocine is classed as an Investigational New Drug by the Food and Drug Administration.

Under Schedule II of this Act, the manufacture, distribution, dispensing or possession with intent to manufacture, distribute or dispense levallorphan is punishable by a prison term not to exceed 15 years and/or a fine not to exceed $25,000. A second conviction can result in the doubling of these penalties. Under Schedule III, the manufacture, distribution, dispensing or possession with intent to manufacture, distribute or dispense nalorphine can result in a term of imprisonment not more than 5 years and/or a fine not to exceed $5,000.

The simple possession of any controlled antagonist (regardless of the schedule under which it falls) is punishable by a term of imprisonment of not more than one year and/or a fine of not more than $5,000. Subsequent offenses of simple possession can result in the doubling of these penalties. In the case of a person who has no prior conviction for any drug offense, the court may, without entering a judgment of guilty and with the consent of such person, defer further proceedings and place him on probation upon such reasonable conditions as it may require for such period (not to exceed one year) as the court may prescribe. Upon completion of the terms of probation, the court shall discharge such person and dismiss proceedings against him.

Issues and Opinions

Despite the proclamations of various individuals and social agencies, most serious researchers do not regard the narcotic antagonists as the complete and ultimate solution to this country's addiction problem. The antagonists are still a relatively recent development in the field of narcotic dependence and much pharmacological and therapeutic research must be carried out before their ultimate value can be assessed.

Antagonists are not the solution to the drug problem. But since the problem seems unlikely to go away, the antagonists, as is true of other methods, can play a potentially important role in treatment. They can be, as one addict put it, "like having a friend in your pocket."

--Allen L. Hammond (1971)

. . . cyclazocine seems useful in the management of narcotics addicts seeking treatment leading to abstinence. Its major role appears to be in helping former addicts maintain abstinence during the first few months following withdrawal. Yet this conclusion is only tentative. Controlled studies are needed to delineate adequately the role of narcotic antagonists in the treatment of addiction.

--J. N. Chappel et al. (1971)

In the clinical trials that have been conducted to date, however, it has been discovered that a number of detoxified addicts who took daily doses of antagonists and received little or no assistance in dealing with their personal and social problems, took refuge in other drugs. The ghetto black, for example, who, while under the influence of cyclazocine could not experience relief from heroin, but who had to return to his oppressive life situation, often becomes dependent upon barbiturates and/or alcohol. But this substitution of drugs entailed greater danger for the individual: barbiturates and alcohol both have high potentials for dependence, and the withdrawal from these sedatives is far more life threatening than is the withdrawal from heroin. In such instances, narcotic antagonists may be responsible for inducing addicts to take up the use of substances which are far more dangerous than heroin.

--STASH Capsules

The narcotic antagonists--cyclazocine and naloxone--have limited value to date, appearing to be chiefly utilized by the addict seeking abstinence. The many problems with these agents--agonist effects in the instance of cyclazocine and variable potency when given orally in the instance of naloxone--remain to be solved. The potential therapeutic value of narcotic antagonists however is enormous. It is likely that the real achievements of the last two decades will be extended and supplemented in the decades to come for we have now a scientific and medical base from which to view these problems in place of the theological-punitive-legal stance of the past.

--E. C. Senay & P. F. Renault (1971)

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